Breast cancer

HER2+ METASTATIC BREAST CANCER

TRIAL SUMMARY: The MARIANNE study

In phase 2 and 3 studies, treatment with both ado-trastuzumab emtansine (T-DM1) and pertuzumab (P) combined with trastuzumab and docetaxel has shown statistically significant increases in progression-free survival (PFS) and overall survival (OS) when compared to standard regimens in patients with HER2-positive metastatic breast cancer (MBC). Moreover, the combination of T-DM1 + P resulted in synergistic inhibition of tumour cell line proliferation in vitro. Based on these findings, patients with advanced HER2-positive breast cancer were randomized (1:1:1) to trastuzumab + a taxane (docetaxel or paclitaxel; HT) vs T-DM1 + placebo or T-DM1 + P in the MARIANNE trial. The primary endpoint was PFS assessed by independent review. Of note, comparisons between each treatment arm were considered separately, and PFS was tested first for noninferiority and subsequently for superiority only if non-inferiority was achieved.

Results: At the time of analysis, 365 patients had been randomized to HT, 367 to T-DM1 and 363 to T-DM1 + P. In each arm, approximately 31% of patients had prior (neo)adjuvant treatment with HER2-directed therapy, and roughly 37% overall had de novo disease. The study met the PFS noninferiority endpoint, but not superiority; OS was similar across treatment arms. These data demonstrate noninferiority in PFS between T-DM1-containing arms and control. T-DM1-containing regimens were associated with a different toxicity profile than the control regimen.

TABLE 3. T-DM1 ± P vs HT in HER2+ MBC

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HT</th>
<th>T-DM1</th>
<th>T-DM1 + P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median followup (mo)</td>
<td>34.8</td>
<td>34.9</td>
<td>34.7</td>
</tr>
<tr>
<td>Median PFS (mo)</td>
<td>13.7</td>
<td>14.1</td>
<td>15.2</td>
</tr>
<tr>
<td>HR (97.5% CI)</td>
<td></td>
<td>0.91 (0.73–1.13), p=0.31 vs HT</td>
<td>0.87 (0.69–1.08), p=0.14 vs HT</td>
</tr>
<tr>
<td>ORR (%)</td>
<td>67.9</td>
<td>59.7</td>
<td>64.2</td>
</tr>
<tr>
<td>Median duration of response (mo)</td>
<td>12.5</td>
<td>20.7</td>
<td>21.2</td>
</tr>
<tr>
<td>Grade 3–5 AEs (%)</td>
<td>54.1</td>
<td>45.4</td>
<td>46.2</td>
</tr>
<tr>
<td>Most common grade 3–5 AEs (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>19.8</td>
<td>4.4</td>
<td>2.7</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>6.5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>2.8</td>
<td>4.7</td>
<td>6.0</td>
</tr>
<tr>
<td>AST increased</td>
<td>0.3</td>
<td>6.6</td>
<td>3.0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0</td>
<td>6.4</td>
<td>7.9</td>
</tr>
</tbody>
</table>

AE=adverse event; AST=aspartate aminotransferase; HR=hazard ratio; HT=trastuzumab + taxane (docetaxel or paclitaxel); ORR=objective response rate; P=pertuzumab; PFS=progression-free survival; T-DM1=ado-trastuzumab emtansine.

COMMENTARY:
Danielle Desautels, MD, FRCPC, Department of Internal Medicine, University of Manitoba; and Debjani Grenier, MD, FRCPC, Medical Oncologist, CancerCare Manitoba

T-DM1 is an antibody-drug conjugate consisting of trastuzumab linked to the microtubule inhibitor DM1. After binding HER2 receptors on the surface of tumour cells, the drug is internalized and the cytotoxic agent released. T-DM1 is an active agent in women with metastatic HER2-positive breast cancer, and was first approved for use in this population in 2013.

In the phase 3 EMILIA study of patients with HER2-positive breast cancer previously treated with trastuzumab and a taxane, T-DM1 was associated with a 6-month improvement in survival compared to the previous standard of care, lapatinib plus capecitabine (median OS 30.9 vs 25.1 months). The phase 3 TH3RESA trial showed that women who had progressed on at least 2 previous HER2-directed therapies, including both trastuzumab and lapatinib, still benefited from T-DM1 when compared to treatment with physician’s choice (median PFS 6.2 vs 3.3 months).

Evidence to support a role for T-DM1 in the first-line metastatic setting came from a randomized phase 2 study in which 137 women with HER2-positive MBC were randomly assigned to trastuzumab plus docetaxel or T-DM1. In this study, patients treated with T-DM1 had a longer time to progression (median PFS 14.2 vs 9.2 months). There were also fewer serious (grade 3/4) adverse events, including those leading to treatment discontinuation. MARIANNE was a well-conceived phase 3 clinical trial designed to confirm these early results. Preclinical evidence of synergy between T-DM1 and pertuzumab prompted inclusion of a pertuzumab-containing arm.

Results from the MARIANNE trial have been highly anticipated by clinicians, as the favourable toxicity profile of T-DM1 makes it an attractive treatment option. Unfortunately, this study demonstrated that neither T-DM1 nor T-DM1 plus pertuzumab are superior to the old standard of care, a taxane plus trastuzumab. Conversely, the final survival analysis of the CLEOPATRA trial demonstrated that the addition of pertuzumab to trastuzumab and
docetaxel in the first-line setting significantly improved survival (median OS 56.5 vs 40.8 months). Given this, the combination of a taxane, trastuzumab and pertuzumab quite clearly remains the first-line standard of care for women with HER2-positive MBC, with T-DM1 reserved for later lines.

References

COMMENDATION:

Sara Soldera, MD, FRCP, Medical Oncology Fellow, McGill University Health Centre; Nathaniel Bouganim, MD, FRCP, Medical Oncologist, McGill University Health Centre; Jamil Asselah, MD, FRCP, Medical Oncologist, McGill University Health Centre

In previous randomized phase 3 trials, T-DM1 has shown efficacy as a single agent for the treatment of HER2-positive locally advanced breast cancer (LABC) or MBC after failure of trastuzumab-based chemotherapy. The TH3RESA trial first reported an improvement in PFS over physician's choice of chemotherapy after the failure of at least 2 HER2-targeted therapies. The EMILIA trial further supported the use of trastuzumab combined with pertuzumab plus docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer. J Clin Oncol 2013; 31:1157.


IN BRIEF

Already known
- Ado-trastuzumab emtansine (T-DM1) and pertuzumab combined with trastuzumab and docetaxel increases progression-free survival (PFS) and overall survival (OS) when compared to standard regimens in patients with HER2-positive metastatic breast cancer (MBC).

What this study showed
- Neither T-DM1 nor T-DM1 plus pertuzumab are superior to the standard of care, a taxane plus trastuzumab.

Next steps
- The combination of a taxane, trastuzumab and pertuzumab remains the first-line standard of care for women with HER2-positive MBC, with T-DM1 reserved for later lines.

CLEOPATRA study, the addition of this molecule to trastuzumab and docetaxel considerably prolonged both PFS and OS. Based on these results and in vitro studies suggesting that these drugs have synergistic activity, a phase 2 trial of combination T-DM1 and pertuzumab was undertaken. The reported objective response rates (ORR) of 41%, median PFS of 6.6 months and acceptable toxicity profile showed promise for this regimen.

The MARIANNE study is an international randomized phase 3 trial that investigated the use of T-DM1 and pertuzumab for the treatment of HER2+ LABC or MBC in patients who had received no prior chemotherapy in this setting, or had completed neoadjuvant or adjuvant chemotherapy ≥6 months before. One thousand and ninety-five patients were randomized to either T-DM1 and placebo (3.6 mg/kg q3wk), T-DM1 and pertuzumab (840 mg loading dose, followed by 420 mg q3wk), or standard treatment with trastuzumab combined with a taxane (docetaxel 75 to 100 mg/m² IV q3wk or paclitaxel 80 mg/m² IV q1wk). The primary endpoint of the trial was PFS by independent review facility, with OS, PFS by investigator, ORR, safety and quality of life (QOL) data as secondary outcomes. Of note, the trial was powered for both noninferiority and superiority analyses of PFS.

The majority of patients recruited to this trial were from Western Europe, Canada or Australia, roughly 65% were ECOG 0, 55% had estrogen and progesterone receptor-positive disease, and approximately 70% had visceral involvement. Roughly 55% of patients had received prior neoadjuvant or adjuvant therapy, and approximately 10% had been previously treated with LABC or MBC therapies (roughly 5% endocrine and 2% HER2-targeted agents). PFS was similar in all therapeutic arms, with a median PFS of 13.7 months, 14.1 months and 15.2 months for standard chemotherapy, T-DM1 alone and T-DM1 combined with pertuzumab, respectively (hazard ratio [HR] 0.91, p=0.31 and HR 0.87, p=0.14). Both experimental arms were found to have a noninferior PFS compared to the control arm, but did not reach superiority, while the addition of pertuzumab to T-DM1 did not improve outcomes. These results were consistent across all subgroup analyses. OS reported at the first interim analysis showed similar results, but the median OS had not yet been reached.

Grade 3 and 4 adverse events occurred earlier and more
frequently with standard chemotherapy (54.1% vs 45.4% and 46.2%), particularly neutropenia, febrile neutropenia, diarrhea, decrease in left ventricular ejection fraction, alopecia, peripheral neuropathies and edema. Anemia, thrombocytopenia, nausea, epistaxis, headache, pyrexia, chills and increased liver enzymes were more frequent in the experimental arms.

In conclusion, the use of T-DM1 with or without pertuzumab did not improve outcomes for patients diagnosed with LABC or MBC in the first-line setting. However, these regimens did show noninferior PFS compared to standard treatment with trastuzumab and taxanes, with more favorable toxicity profiles. The addition of pertuzumab to T-DM1 failed to show benefit, contradicting previous reports that hypothesized a synergy between these 2 drugs.

References